the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Status of the Claims.

Claims 24, 26-35, 37-38, 40, and 42-45 are pending with entry of this amendment, claims 1-23, 25, 36, 39, 41, and 46-71 being cancelled, and no claims being added herein. Claims 24, 26, 27, 30, 32, 40, 42, 43, 44, and 45are amended herein. These amendments introduce no new matter. Most the amendments limit the claims to the elected species and/or make grammatical or spelling corrections per the Examiner request Support is replete throughout the specification (*e.g.*, in the claims as filed, section B at page 22, and the like.

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 1-23, and 51-71 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Priority.

The Examiner indicated that the instant application is granted the benefit of priority for the U.S. Provisional Application No: 60/115,434, filed on January 6, 1999. The Examiner alleged, however, that ORF28, an O-methyltransferase in theC-1027 gene cluster, does not appear to be disclosed in the provisional application. The Examiner further stated that since methods using this ORF are the elected subject matter, none of the claims are granted priority to this date.

Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449).

Drawings.

The drawings were considered informal for the reasons detailed in the attached copy of PTO Form 948. Corrected formal drawings are submitted with this amendment.

Sequence Listing Rules.

The Examiner indicated that the application is not in compliance with sequence rules, 37 C.F.R. §§ 1.821-1.825. In particular, the examiner noted that in figure 7, a consensus sequence is disclosed that is not identified by a sequence identification number. A disk containing a substitute sequence listing containing the referenced sequence(s) in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk are provided herewith. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Objections to the specification.

The title was objected to for allegedly not complete describing the claimed subject matter. In accordance with the Examiner's recommendation, Applicants have amended the title with entry of this amendment thereby obviating this objection.

The specification was objected to for allegedly being confusing as described below:

A) Table I and II.

The Examiner alleged that Tables I and II cite a relative nucleotide position, but it was allegedly unclear which SEQ I NO these relative positions relate to. Tables I and II are amended herein to clarify that the position is with respect to SEQ ID NO:1.

B) Page 29, line 28.

The Examiners alleged that on page 29, line 28, the specification (section E) refers to benzoxazolinates, not beta amino acids. Applicants note that the section identified by the Examiner correctly recites Benzoxazolinates. Beta amino acids are correctly identified in the preceding section (Section D) beginning on page 29, line 10.

C) Epoxide hydrase.

The Examiner alleged that the terms "epoxide hydrase and "epoxide hydrolase" are used somewhat interchangeably through the specification and requested consistent claim language for clarity. The claims as amended herein contain neither the term "epoxide hydrase nor the term "epoxide hydrolase" thereby obviating this objection.

D) Table II, ORF 28.

The Examiner alleged that in Table II, ORF28 is disclosed as being 335 amino acids long while in Figure 3B, ORF 28 is describe ed as being 350 amino acids long. Applicants believe the listing in Table II is correct and the 350 aa reference in Figure 3B is a typographical error.

Objections to the Claims.

Claims 24-50 were objected to for containing non-elected subject matter. Per the Examiner's request, the claims are amended herein so that they are drawn only to elected subject matter.

Claim 25 was objected to under 37 C.F.R. §1,75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 25 is cancelled herein thereby obviating this objection. Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellation should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Claims 26 and 27 were objected to for using improper verb tenses. These claims have been amended to replace the term "comprising" with the term --comprises-- thereby obviating this objection.

Claim30 was objected to because of the missing "is" before "*ex vivo*". Claim 30 is amended herein to insert the "is" thereby obviating this objection.

Claim 32 was objected to for the use of the adjective exogenous. Claim 32 is amended herein to replace the adjective with the adverb --exogenously-- thereby obviating this objection.

Claim 36 was objected to under 37 C.F.R. §1,75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 36 is canceled with entry of this amendment thereby obviating this objection.

Claim 39 was objected to as allegedly being a duplicate of claim 30. Claim 39 is canceled with entry of this amendment thereby obviating this objection.

Claim 40 was objected to from improper English. The work --least--has been inserted before the word --substantially-- thereby obviating this objection.

Claim 41 was objected to for a typographical error. Claim 41 is canceled with entry of this amendment thereby obviating this objection.

Claims 41-42 were objected to for a typographical error. Claim 41 is canceled with entry of this amendment while claim 42 is amended herein eliminating the misspelled word "sulfer" thereby obviating this objection.

35 U.S.C. §112, Second Paragraph.

Claims 24-50 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons summarized below:

Office Action Item 20: Claims 24-50.

Claims 24-50 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner claim 24 was unclear as to whether the claims are limited to the polypeptide encoded by SEQ ID NO:2, 4188-5189 bp or whether the claims read on an O-methyltransferase from any enediyne-synthesizing organisms. Claim 24, as amended clarifies that the O-methyltransferase is an "O-methyltransferase encoded by a *Streptomyces* C-1027 biosynthesis gene cluster open reading frame 28". Accordingly, the rejection of claims 24-50 under 35 U.S.C. §112, second paragraph, on these grounds should be withdrawn.

Office Action Item 21: Claim 40.

Claim 40 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, of the use of the term "substantially". According to the Examiner the term "substantially" is a relative term. Applicants traverse.

It is well accepted that terms of approximation, such as "substantially" are permissible in patent claims and do not render such claims indefinite. For example, as stated by the Court of Appeals of the Federal Circuit:

> We note that like the term "about," the term "**substantially**" is a descriptive term **commonly used in patent claims** to "avoid a strict numerical boundary to the specified parameter." Pall Corp. v. Micron Seps., 66 F.3d 1211, 1217, 36 USPQ2d 1225, 1229 (Fed. Cir. 1995); See, e.g., Andrew Corp. v. Gabriel Elecs. Inc., 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988) **(noting that terms such as "approach each other," "close to," "substantially equal," and "closely approximate" are ubiquitously used in patent claims and that such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior**

> **art, have been accepted in patent examination and upheld by the courts**). In this case, "substantially" avoids the strict 100% nonuniformity boundary. [emphasis added] *Echolab Inc. v Envirochem Inc.*, ___USPQ2d ___ (No. 00-1402 Federal Circuit, Sept. 6, 2001).

In view of the fact that controlling legal authority recognizes the use of terms of approximation in patent claims as proper and definite, Applicants submit that the rejection under 35 U.S.C. §112, second paragraph, on these grounds is improper and should be withdrawn.

Office Action Item 22: Claim 40.

Claim 40 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, of the use of the term "enediyne analogue". Applicants traverse.

The Examiner is reminded that a claim is definite if "... read in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *In re Jackson,* 217 USPQ. 804, 806 (BPAI, 1982).

The term analogue as used in the context of "enediyne analogue" is a term well understood by those of skill in the art. Chemicals and chemical analogues are commonly recognized and distinguished by those of ordinary skill in the art. In addition, Applicants note the term "analogue" is one frequently allowed by the Patent Office in various claims. Thus, for example: U.S. Patent 6,448,392 claims "[a] liponucleoside compound comprising an antiviral **nucleoside analogue**. . . ", U.S. Patent 5,962,532 claims ". . . b) injecting into the site **capsaicin or capsaicin analogue** in a dosage formulation having a concentration between about 0.01 and 10% by weight capsaicin. . . ", U.S. Patent 6,232,346 claims ". . . the method comprising administering to a mammal an effective amount of a carrier and a nutritional supplement comprising L-Carnitine or its functional **analogue**, Coenzyme Q10 (Ubiquinone) or its functional **analogue** and Taurine or a Taurine precursor in a single or divided daily dose.", U.S. Patent 6,319,512 claims "7. The implant for the controlled release of at least one pharmaceutically active principle according to claim 1, wherein the active principle is an **analogue of somatostatin** or of one of the pharmaceutically acceptable salts thereof.", and so forth.

The use of the term "enediyne analogue" reasonably apprises one of skill in the art of the scope of the invention and is as precise as the subject matter permits. This rejection under 35 U.S.C. §112, second paragraph, should therefore be withdrawn.

Office Action Item 23: Claims 41-45.

Claims 41-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner, the term "hydrase" in claims 41 and 42 was unclear. Claim 41 is cancelled and the term "hydrase" is eliminated from claim 42 with entry of this amendment thereby obviating this rejection. The claim cancellation, however, should not be construed as abandonment or agreement with the Examiner's position in the Office Action and Applicants reserve the right to file subsequent applications claiming the canceled subject matter.

Office Action Item 24: Claims 41-45.

Claims 41-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner, the term "proline oxidase" in claims 41 and 42 was unclear. Claim 41 is cancelled and the term "praline oxidase" is eliminated from claim 42 with entry of this amendment thereby obviating this rejection. The claim cancellation, however, should not be construed as abandonment or agreement with the Examiner's position in the Office Action and Applicants reserve the right to file subsequent applications claiming the canceled subject matter.

Office Action Item 25: Claims 41-45.

Claims 41-45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, of the references to various enzyme activities in claims 41 and 42. Claim 41 is cancelled and the references to various enzyme activities are eliminated from claim 42 with entry of this amendment thereby obviating this rejection. The claim cancellation, however, should not be construed as abandonment or agreement with the Examiner's position in the Office Action and Applicants reserve the right to file subsequent applications claiming the canceled subject matter.

Office Action Item 26: Claim 45.

Claim 45 was rejected under 35 U.S.C. §112, second paragraph, as indefinite because the purpose of the limitation of "ORF 3" in claim 45 was allegedly unclear. The Examiner alleged that

the purpose of the limitation of ORF 3 is already found in the parent claim 44. Claim 44 presently recites ". . . wherein said biological molecule is additionally contacted with polypeptides encoded by ORF 15, ORF 16, ORF3, ORF 14, and ORF 13.". This claim contains no reference either to ORF 28 or to ORF 3. Accordingly, the purpose of the limitation of ORF 3 is not found in the parent claim, and claim 45 is a proper dependent claim.

Office Action Item 27: Claims 46-50.

Claims 46-50 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, of the form of the references to enzyme names. Claim 46-50 are cancelled with entry of this amendment thereby obviating this rejection. The claim cancellations, however, should not be construed as abandonment or agreement with the Examiner's position in the Office Action and Applicants reserve the right to file subsequent applications claiming the canceled subject matter.

35 U.S.C. §112, First Paragraph, Written Description.

Claims 24-50 were rejected under 35 U.S.C. §112, first paragraph, written description as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleged that the specification does not adequately describe other O-methyltransferases from other enediyne gene clusters as well as using other biological molecules as substrates. Applicants respectfully traverse.

As stated in *Union Oil Co. of California v. Atlantic Richfield Co.*, 54 USPQ2d 1227 (CAFC 2000), the "written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description **must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed**.'" *Id.* at 1232 (citation omitted). The primary purpose of this requirement is to ensure that the specification clearly conveys to one skilled in the art what the applicant regarded as his or her invention when the application was filed. This requirement serves the public policy of limiting the ability of an applicant to later claim subject matter that, while enabled by the specification, was not identified in the specification as the applicant's invention. **The description requirement does not, however, include a requirement that a patent**

applicant "disclose every species encompassed by their claims." *In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

Rather, as the Federal Circuit recently reiterated:

> [T]he language of the specification...**must describe the claimed invention so that one skilled in the art can recognize what is claimed**." [emphasis added] *Enzo Biochem, Inc. v. Gen-Probe Incorporated.* ____ F.3d ____. (Fed. Cir. July 15, 2002; 01-1230).

Put another way:

> One skilled in the art, reading the original disclosure, **must reasonably discern the limitation at issue in the claims**. *Waldemar Link GmbH & Co. v. Osteonics Corp.*, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994).

Claims 24-50, as amended herein, are directed to methods that utilize a "**an O-methyltransferase** encoded by a ***Streptomyces*** C-1027 biosynthesis gene cluster open reading frame **28"**. One skilled in the art, reading the original disclosure would reasonably discern the limitation "a Streptoymnces C-1027 biosynthesis gene cluster open reading frame 28" in the original disclosure. Accordingly, Applicants have met the description requirement with respect to this limitation and the rejection under 35 U.S.C. §112, first paragraph, written description grounds should be withdrawn.

Similarly, with respect to the substrate limitation, one suitable substrate for O-methyltransferase is illustrated in Figure 3B. One of ordinary skill in the art would recognize a number of other analogues of the illustrated substrate that would also be suitable for modification by O-methyltransferase. Moreover, one skilled in the art, reading the original disclosure would reasonably discern the use of O-methyltranasferase with other substrates. Accordingly, Applicants have met the description requirement with respect to this limitation and the rejection under 35 U.S.C. §112, first paragraph, written description grounds should be withdrawn.

35 U.S.C. §112, First Paragraph, Scope of Enablement..

Claims 24-27, 30, 37, 39, 40-50 were rejected under 35 U.S.C. §112, first paragraph, scope of enablement. In particular, the examiner alleged that the specification while enabling for *ex vivo* methods using only the O-methyltransferase, does not reasonably provide enablement of ex vivo methods using more than one enzyme form the gene cluster. Applicants traverse.

The Examiner is respectfully reminded that to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention . **That some experimentation is necessary does not constitute a lack of enablement**; the amount of experimentation, however, must not be unduly extensive.

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) *citing Ex parte Forman Inc.,* 230 USPQ 546 (BPAI 1986).

Applicants note the Examiner has already acknowledged that the specification is enabling for *ex vivo* methods using only the O-methyltransferase (*see* Office Action, page 14, item 29). Is the Examiner asserting that an *ex vivo* method utilizing, for example one more enzyme from the C-1027 biosynthetic cluster or even two or three more enzymes would really require undue experimentation? Applicants submit that such methods are a straightforward extension of methods utilizing one enzyme (*e.g.* O-methyltransferase) and require, at most, only routine experimentation.

Moreover, with respect to the In re Wands factors, Applicants note that relatively little experimentation (Wands Factor 1) is necessary. The combination of enzymes can readily be screened ex vivo in a standard physiologic buffer system with the appropriate substrate(s). This is at most, routine screening. The specification provides considerable guidance (Wands Factor 2) with respect to C-1027 polypeptide activities and the appropriate substrates and reaction pathways (*see, e.g.,* Figures 1, 2, 3A, 3B, 4, and the like). Working examples (Wands Factor 3) are provided. The nature of the invention is relatively straightforward (Wands Factor 4) being directed to the use of C-1027 enzyme(s) to chemically modify target substrates. The state of the prior art is well developed (Wands Factor 5): PKSs and NRPSs are well known to those of skill in the art (see e.g.. background section) and the *ex vivo* use of combinations of enzymes to modify various substrates is very well developed. The level of skill of those in the art (Wands Factor 6) is high, typically Ph.D. The predictability of the art (Wands Factor 7) is good, PKS pathways have been shown to have interchangeable modules and the same is true for NRPS pathways and hundreds of enzymes have been demonstrated to function *ex vivo.* In

addition, the claims are relatively narrow (Wands Factor 8), pertaining specifically to methods of modifying substrates using C-1027 polypeptides.

All of the factors recited in *In re Wands* indicate that performance of the claimed methods requires no undue experimentation. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

35 U.S.C. §101.

Claims 24-27, 38, and 40-50 were rejected under 35 U.S.C. §101 as directed to non-statutory subject matter because the "hand of man" allegedly has not been incorporated into the instant claim language. Claim is amended herein to recite:

> 24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for an O-methyltransferase encoded by a C-1027 biosynthesis gene cluster open reading frame 28 (ORF 28), with an O-methyltransferase encoded by a C-1027 biosynthesis gene cluster open reading frame 28, **where said O-methyltransferase is expressed by a vector comprising a nucleic acid encoding said O-methyltransferase**, said contacting resulting in the chemical modification of said biological molecule. [emphasis added'

The language "**where said O-methyltransferase is expressed by a vector**" indicates that the polypeptide is a recombinantly expressed polypeptide. The method thus does not occur in nature and the rejection under 35 U.S.C §101 should be withdrawn.

35 U.S.C. §103(a).

Claims 24-27, 38, and 40-50 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Hu *et al.* (1994) *Mol. Microbiol.,* 14: 163-172. According to the Examiner , the instant claims are drawn to methods of modifying a biological molecule using polypeptides of the C-1028 biosynthetic gene cluster in a bacterial cell. According to the Examiner, one of skill would have been motivated to use *S. globisporus* C-1027 to produce its product antibiotic C-1027 thereby practicing the claimed methods. Applicants respectfully traverse.

A *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.,* 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the instant case, the cited art (Hu *et al.*) fails to teach or suggest the limitations of the presently claimed invention. Claim 1, as amended herein recites:

> 24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for an O-methyltransferase encoded by a C-1027 biosynthesis gene cluster open reading frame 28 (ORF 28), **with an O-methyltransferase encoded by a *Streptomyces* C-1027 biosynthesis gene cluster open reading frame 28, where said O-methyltransferase is expressed by a vector comprising a nucleic acid encoding said O-methyltransferase**, said contacting resulting in the chemical modification of said biological molecule.

Hu *et al.* fails to teach or suggest a method involving the use of an O-methyltransferase expressed by a vector. To the contrary, Hu *et al.* is simply an article describing the use of streptomyces to produce the antibiotic C-1027 **in a fermentation process** (*see, e.g.,* page 1578). Hu *et al.* do not appear to have isolated the C01027 biosynthetic gene cluster nor have they identified any of the gene cluster's constituent open reading frames (ORFs).

Lacking any teaching or suggestion whatsoever regarding the nucleic acid/amino acid sequences comprising the C-1027 biosynthetic gene cluster, Hu *et al.* cannot teach or suggest a method that involves expressing the C-1027 O-methyltransferase using a vector.

The Examiner has therefore failed to make his prima facie case, with respect to the amended claims, and the rejection under 35 U.S.C. §103(a) should be withdrawn.

Double Patenting.

The Examiner indicated that should claim 30 be found allowable, claim 39 will be objected to under 37 C.F.R. §1.75 as being a substantial duplicate thereof. Claim 39 is canceled with entry of this amendment thereby obviating this potential objection.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/478,188 WITH ENTRY OF THIS AMENDMENT

In the specification:

Page 14. lines 17-22:

Figure 7 shows the amino acid sequence alignment of SgcA (SEQ ID NO:113) with three other dNDP-glucose 4,6-dehydratases. Gdh, TDP-glucose 4,6-dehydratase of *S. erythraea* (AAA68211) (SEQ ID NO:115); MtmE, TDP-glucose 4,6-dehydratase in the mithramycin pathway of *S. argillaceus* (CAA71847) (SEQ ID NO:117); TylA2, TDP-glucose 4,6-dehydratase in the tylosin pathway of *S. fradiae* (S49054) (SEQ ID NO:116). Given in parentheses are protein accession numbers. The αβα fold with the NAD^+-binding motif of GxGxxG is boxed. **Consensus sequence is SEQ ID NO:119.**

Page 16, row 1 of Table I:

orf #	Size	Relative position (In SEQ ID NO: 1)	Primers	Function	Seq ID No.

Page 18, row 1 of Table II:

ORF	Relative Position (In SEQ ID NO: 1)	Primers	Function	SEQ ID NO.

In the claims:

24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for a**n O-methyltransferase** encoded by a C-1027 biosynthesis gene cluster open reading frame **28 (ORF 28)**, with a**n O-methyltransferase** encoded by a ***Streptomyces*** C-1027 biosynthesis gene cluster open reading frame **28, where said O-methyltransferase is expressed by a vector comprising a nucleic acid encoding said O-**

methyltransferase, [~~whereby said polypeptide chemically modifies~~] said contacting resulting in the chemical modification of said biological molecule.

26. The method of claim 24, wherein said method **[comprising] comprises** contacting said biological molecule with **said O-methyltransferase and** at least **[two different]one additional** polypeptide[s]encoded by **a** C-1027 biosynthesis gene cluster open reading frame**[s]**.

27. The method of claim 24, wherein said method **[comprising]further comprises** contacting said biological molecule with **said O-methyltransferase and** at least [three different] **two additional** polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames.

30. The method of claim 24, wherein said contacting **is** ex vivo.

32. The method of claim 28, wherein said biological molecule is an exogenous**ly** supplied metabolite.

40. The method of claim 24, wherein said method comprises contacting said biological molecule with at **least** substantially all of the polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames and said method produces an enediyne or enediyne analogue.

42. The method of claim 41, wherein said biological molecule is a fatty acid**[~~-and said biological molecule is contacted with a plurality of C-1027 orf polypeptides comprising an epoxide hydrase, a monooxygenase, an iron-sulfer flavoprotein, a p-450 hydroxylase, an oxidoreductase, and a proline oxidase~~]**.

43. The method of claim 42, wherein said biological molecule is **additionally** contacted with polypeptides encoded by ORF17, ORF20, ORF21, ORF29, ORF30, ORF32, ORF35, and ORF38.

44. The method of claim 41, wherein said biological molecule is **additionally** contacted with polypeptides encoded by ORF 15, ORF 16, ORF 28, ORF3, ORF 14, and ORF 13.

45. The method of claim 44 wherein said biological molecule is [also]**additionally** contacted with polypeptides encoded by ORF 4 and ORF 3.

APPENDIX B

CLAIMS PENDING IN USSN 09/478,188 WITH ENTRY OF THIS AMENDMENT

24. A method of chemically modifying a biological molecule, said method comprising contacting a biological molecule that is a substrate for an O-methyltransferase encoded by a C-1027 biosynthesis gene cluster open reading frame 28 (ORF 28), with an O-methyltransferase encoded by a *Streptomyces* C-1027 biosynthesis gene cluster open reading frame 28, where said O-methyltransferase is expressed by a vector comprising a nucleic acid encoding said O-methyltransferase, said contacting resulting in the chemical modification of said biological molecule.

26. The method of claim 24, wherein said method comprises contacting said biological molecule with said O-methyltransferase and at least one additional polypeptide encoded by a C-1027 biosynthesis gene cluster open reading frame.

27. The method of claim 24, wherein said method further comprises contacting said biological molecule with said O-methyltransferase and at least two additional polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames.

28. The method of claim 24, wherein said contacting is in a host cell.

29. The method of claim 28, wherein said host cell is a bacterium.

30. The method of claim 24, wherein said contacting is ex vivo.

31. The method of claim 28, wherein said biological molecule is an endogenous metabolite produced by said host cell.

32. The method of claim 28, wherein said biological molecule is an exogenously supplied metabolite.

33. The method of claim 28, wherein said host cell is a eukaryotic cell.

34. The method of claim 33, wherein said eukaryotic cell is selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

35. The method of claim 28, wherein said host cell synthesizes sugars and glycosylates the biological molecule.

37. The method of claim 24, wherein said method further comprises contacting said biological molecule with a polyketide synthase or a non-ribosomal polypeptide synthetase.

38. The method of claim of claim 24, wherein said contacting is in a bacterial cell.

40. The method of claim 24, wherein said method comprises contacting said biological molecule with at least substantially all of the polypeptides encoded by C-1027 biosynthesis gene cluster open reading frames and said method produces an enediyne or enediyne analogue.

42. The method of claim 41, wherein said biological molecule is a fatty acid.

43. The method of claim 42, wherein said biological molecule is additionally contacted with polypeptides encoded by ORF17, ORF20, ORF21, ORF29, ORF30, ORF32, ORF35, and ORF38.

44. The method of claim 41, wherein said biological molecule is additionally contacted with polypeptides encoded by ORF 15, ORF 16, ORF3, ORF 14, and ORF 13.

45. The method of claim 44 wherein said biological molecule is additionally contacted with polypeptides encoded by ORF 4 and ORF 3.